# Disease Stage and Mode of Therapy Are Important Determinants of Treatment Outcomes for Medication-Related Osteonecrosis of the Jaw

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**Purpose:** The treatment of patients with medication-related osteonecrosis of the jaw (MRONJ) is challenging. The purpose of the present study was to estimate the frequency and identify the factors associated with clinical improvement during treatment.

**Patients and Methods:** We designed and implemented a retrospective cohort study and enrolled a sample of subjects diagnosed with MRONJ between 2004 and 2015. The primary predictor variables were a set of heterogeneous variables grouped into the following categories: demographic (age and gender) and clinical (location of necrosis, therapy duration, medication type, disease stage, and treatment type). The primary outcome variable was the treatment outcome, defined as stable or worse and improved or healed. The descriptive, bivariate, and multiple logistic statistics were computed, and statistical significance was defined as $P < .05$.

**Results:** The sample included 337 subjects with a mean age of 68.9 years. Of the 337 subjects, 256 were women (76%). A total of 143 patients (42.2%) experienced spontaneous necrosis. Twenty-four (7.1%) had had exposure to targeted antiangiogenic agents. Those with stage 1 or 2 disease were more likely to have better outcomes than those with stage 3 disease (stage 1, adjusted odds ratio [OR] 3.4, $P = .005$; stage 2, adjusted OR 2.2, $P = .03$). Treatment type was a significant variable. Subjects undergoing surgery were 28 times more likely to have a positive outcome than those receiving nonoperative therapy (adjusted OR 28.7, $P < .0001$).

**Conclusions:** Subjects with MRONJ who presented with less severe disease or who underwent operative treatment were most likely to have improvement or complete healing of their MRONJ-related lesions.

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Osteonecrosis of the jaw (ONJ) related to antiresorptive medications has received considerable attention in the scientific and lay communities since it was first described more than 10 years ago. The relationship between antiresorptive therapy and ONJ was established in 2001, following an influx of patients to our facility with exposed, necrotic bone isolated to the jaws. These patients were mostly cancer patients who had received chemotherapeutic regimens that varied widely in accordance to the tumor type and characteristics. The only evidence that linked these cases was a history of antiresorptive therapy. The occurrence of necrotic bone in osteoporotic patients receiving oral antiresorptive therapy with no history of cancer or chemotherapy formed a convincing association between jaw necrosis and antiresorptive therapy. In 2004, our institution published the first peer-reviewed report characterizing the clinical

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presentation, suspected pathophysiology, and associated risk factors within a cohort of patients who had been exposed to bisphosphonates.[1] At that time, a relational database (Microsoft Access) was designed to capture various aspects of this disease process, including clinical, epidemiologic, and treatment outcomes data. As new parameters of ONJ presentation and treatment emerged during the previous 10 years (ie, medications, treatment strategies), new data points were appended to the database.

The purposes of the present study were to *1)* describe the characteristics of a sample of patients with medication-related ONJ (MRONJ), *2)* identify the factors associated with the development of MRONJ, and *3)* identify the variables associated with favorable outcomes. We hypothesized that one or more variables would be associated with favorable outcomes for patients with MRONJ. Our specific aims were to *1)* summarize the descriptive statistics of the sample and *2)* examine the factors associated with the outcome (healed or improved vs stable or worse) after treatment of MRONJ.

## Patients and Methods

### STUDY DESIGN AND SAMPLE

We designed and implemented a retrospective cohort study and enrolled a sample derived from the population of subjects with a diagnosis of MRONJ who had received treatment between 2004 and 2015. The sample inclusion criteria were a diagnosis of MRONJ according to the clinical and radiographic findings (Table 1) and a follow-up duration of at least 6 months. The exclusion criteria for this sample were exposure to radiation therapy focused on the head and neck region, medication dosage or duration that could not be verified, malignant disease that directly involved the jaws, and an insufficient follow-up duration. This study met the criteria for exemption by the institutional review board.

### STUDY VARIABLES

*Predictor Variables*

The predictor study variables included a heterogeneous group of variables segregated into the following categories: *1)* demographic, *2)* clinical data, and *3)* treatment modality. The demographic variables included gender and age at MRONJ diagnosis, the indication for antiresorptive or antiangiogenic therapy (malignant or nonmalignant disease), the medication used (bisphosphonate, receptor activator of nuclear factor kappa-B ligand inhibitor, or antiangiogenic agent), duration of exposure, steroid therapy, anatomic location of the exposed bone (maxilla or mandible, or both), and the disease stage at presentation. The disease stage was determined using the American Association of Oral and Maxillofacial Surgeons (AAOMS) staging criteria (Table 1).[2] The treatment types were surgery (alveolectomy or marginal or segmental resection) and nonoperative therapy (systemic antibiotics, antimicrobial rinses). The subjects were followed up continuously until the endpoint of death, the establishment of healed bone, or loss to follow-up.

**Table 1. AAOMS STAGING FOR MRONJ**

| Stage | Description |
|---|---|
| 0 | No clinical evidence of necrotic bone, but nonspecific clinical findings, radiographic changes, and symptoms present |
| 1 | Exposed and necrotic bone or a fistula that probes to bone in asymptomatic patients with no evidence of infection |
| 2 | Exposed and necrotic bone or a fistula that probes to bone, associated with infection, evidenced by pain and erythema in region of exposed bone with or without purulent drainage |
| 3 | Exposed and necrotic bone or a fistula that probes to bone in patients with pain, infection, and ≥1 of the following: exposed and necrotic bone extending beyond the region of alveolar bone (ie, inferior border and ramus in mandible, maxillary sinus, and zygoma in the maxilla), resulting in pathologic fracture, extraoral fistula, oral antral/oral nasal communication, or osteolysis extending to the inferior border of the mandible of the sinus floor |

Abbreviations: AAOMS, American Association of Oral and Maxillofacial Surgeons; MRONJ, medication-related osteonecrosis of the jaw.

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*Outcome Variable*

The treatment outcome was the primary outcome variable and was grouped as stable or worse and improved or healed. The patients were considered healed if complete mucosalization of the exposed bone had occurred with pain relief. The patients were considered improved if they were symptomatically better or had moved to a lower disease stage after treatment. The subjects were considered stable if their disease had not advanced to a higher stage. For patients with stage 1 disease, this was considered a positive outcome, because patients with stage 1 disease are, by definition, asymptomatic. The patients' status was considered worse if they demonstrated progressive pain, infection, or persistent bone exposure after treatment, with advancement to a higher stage.

### STATISTICAL ANALYSIS

A Microsoft Access database was used for data collection and storage. The descriptive and analytic statistics were computed. For each factor of interest, logistic regression analysis was used to examine the association between the outcomes and that factor. All factors were then included in a multivariable logistic regression analysis to examine the joint effects of those factors on the outcome. Backward selection was used to remove variables that did not contribute significant information to the model. Statistical significance was set at $P < .05$.

## Results

From 2004 to 2015, 420 patients with MRONJ were evaluated and treated. Of these patients, 77 were lost to follow-up. An additional 4 patients had information missing (eg, age at diagnosis) and were also excluded from additional analysis. The final study sample included 337 subjects. A summary of the descriptive statistics of the study sample with the associated demographic and clinical characteristics is presented in Table 2. Of the 337 patients, 81 were men (24.0%) and 256 were women (76.0%), with a mean age of 68.9 ± 11.1 years. The diagnoses associated with ONJ were predominantly malignant disease, with 234 patients (69.4%) presenting with cancer. Intravenous or subcutaneous medications were associated with necrosis in 246 patients (73.0%). Zoledronic acid was the most common drug associated with necrosis, representing 193 of the database subjects (57.3%). Pamidronate exposure was noted in 64 (19.0%), oral bisphosphonates in 98 (29.1%), denosumab in 34 (10.1%), and antiangiogenic agents in 24 (7.1%). Of the 337 patients, 254 (75.4%) presented with necrotic bone localized to the mandible, 68 (20.2%) had exposed maxillary bone, and 15 (4.5%) had disease in both jaws. The duration of antiresorptive exposure before disease presentation varied according to the potency of the antiresorptive medication. Monthly denosumab administration had the shortest exposure among the cancer therapies (mean 18.4 months), followed by zoledronic acid (mean 26.4 months), and pamidronate (mean 34.8 months). In the setting of nonmalignant disease, oral bisphosphonates as a group had the longest exposure (mean 69.0 months), and denosumab (Prolia) had the shortest exposure (mean 16.0 months), but that group only included 7 patients. The duration of exposure for the antiangiogenic medications within the context of cancer therapy was the lowest (mean 12.6 months), but represented a small number of patients (n = 11). The limited number of subjects in that group prevented additional analysis regarding the relationship of antiangiogenic treatment and outcomes. Spontaneous bone exposure was noted in 143 subjects (42.5%) and 194 (57.5%) developed bone exposure after surgical trauma. The stage at presentation, defined using the recent AAOMS guidelines[2] (Table 1), was recorded in the database, along

**Table 2. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS**

| Characteristic | Value |
|---|---|
| Sample size | 337 (100) |
| Gender | |
| Female | 256 (76.0) |
| Male | 81 (24.0) |
| Age | 68.9 ± 11.1 |
| Indication for medication | |
| Malignant disease | 234 (69.5) |
| Nonmalignant disease | 103 (30.5) |
| Medication risk factors* | |
| Pamidronate | 64 (19.0) |
| Zoledronic | 193 (57.3) |
| Denosumab (Xgeva) | 34 (10.1) |
| Denosumab (Prolia) | 7 (2.1) |
| Other (oral BP) | 98 (29.1) |
| Antiangiogenic agents | 24 (7.1) |
| Steroid therapy | 59 (17.5) |
| Mode of delivery | |
| IV/SQ | 246 (73.0) |
| PO | 99 (29.4) |
| Anatomic location | |
| Mandibular | 254 (75.4) |
| Maxillary | 68 (20.2) |
| Maxilla and mandible | 15 (4.5) |
| Treatment duration | |
| Pamidronate | 34.8 ± 25.4 |
| Zoledronate | 26.4 ± 22.2 |
| Denosumab (Xgeva) | 18.4 ± 16.2 |
| Denosumab (Prolia) | 16.0 ± 7.3 |
| Other (oral BP) | 69.0 ± 39.9 |
| Antiangiogenic agents | 12.6 ± 14.1 |
| Etiology of MRONJ | |
| Surgery/trauma | 194 (57.5) |
| Spontaneous | 143 (42.5) |
| Disease stage | |
| 1 | 82 (24.3) |
| 2 | 163 (48.4) |
| 3 | 92 (27.3) |
| Treatment modality | |
| Operative | 178 (53.0) |
| Nonoperative | 159 (47.0) |

Data presented as n (%) or mean ± standard deviation.

Abbreviations: BP, bisphosphonate; IV/SQ, intravenous/subcutaneous; MRONJ, medication-related osteonecrosis of the jaw; PO, oral.

* Sums to >100% because some patients used multiple medications.

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with the outcomes to the various operative and nonoperative therapies. Patients with stage 0 disease represented the smallest group with only 3 subjects (1%) and therefore were not included in the analysis. A total of 82 patients (24.3%) had stage 1 disease, 163 (48.4%) presented with stage 2 disease, and 92 (27.3%) had stage 3 disease. The treatment groups were close to an even distribution, with 159 (47%) receiving nonoperative care and 178 (53%) receiving operative care.

The descriptive statistics by outcome are listed in Table 3. The outcome groups were categorized according to the response to the various modes of therapy. A total of 196 patients (58%) were considered healed or improved and 141 (42%) were considered stable or worse. An unexpected finding was that

**Table 3. STUDY VARIABLES GROUPED BY TREATMENT OUTCOME**

| Variable | Improved/Healed | Stable/Worse | *P* Value |
|---|---|---|---|
| Sample size | 196 | 141 | NA |
| Age | | | .006* |
| Mean ± SD | 70.4 ± 10.8 | 66.8 ± 11.2 | |
| Median (IQR) | 70.0 (63.0, 78.0) | 66.0 (59.0, 76.0) | |
| Treatment duration† (mo) | | | .14* |
| Mean ± SD | 45.9 ± 36.9 | 38.8 ± 30.5 | |
| Median (IQR) | 36.0 (18.0, 60.0) | 30.0 (16.0, 60.0) | |
| Categorical factors | | | |
| Gender | | | .0662‡ |
| Male | 40 (20.4) | 41 (29.1) | |
| Female | 156 (79.6) | 100 (70.9) | |
| Indication for medication | | | .029‡ |
| Malignancy | 127 (64.8) | 107 (75.9) | |
| Osteoporosis or other | 69 (35.2) | 34 (24.1) | |
| Steroid therapy | | | .335‡ |
| Yes | 31 (15.8) | 28 (19.9) | |
| No | 165 (84.2) | 113 (80.1) | |
| Mode of delivery | | | |
| IV/SQ | | | .012‡ |
| Yes | 133 (67.9) | 113 (80.0) | |
| No | 81 (41.1) | 36 (25.4) | |
| PO | | | .001‡ |
| Yes | 71 (36.2) | 28 (19.9) | |
| No | 125 (63.8) | 113 (80.1) | |
| Anatomic location | | | .007‡ |
| Mandibular necrosis | 142 (72.4) | 112 (79.4) | |
| Maxillary necrosis | 49 (25.0) | 19 (13.5) | |
| Maxilla and mandible | 5 (2.6) | 10 (7.1) | |
| Etiology of MRONJ | | | .97‡ |
| Surgery/trauma | 113 (57.6) | 81 (57.4) | |
| Spontaneous | 83 (42.4) | 60 (42.6) | |
| Disease stage | | | .338‡ |
| 1 | 42 (21.4) | 40 (28.4) | |
| 2 | 99 (50.5) | 64 (45.4) | |
| 3 | 55 (26.1) | 37 (26.2) | |
| Treatment modality | | | <.0001‡ |
| Operative | 156 (79.6) | 22 (15.6) | |
| Nonoperative | 40 (20.4) | 119 (84.4) | |

Data presented as n (%), unless otherwise noted.

Abbreviations: IQR, interquartile range; IV/SQ, intravenous/subcutaneous; MRONJ, medication-related osteonecrosis of the jaw; NA, not applicable; PO, oral; SD, standard deviation.

* Mann-Whitney test.

† Data available for 182 subjects with improved or healed outcomes and 122 with stable or worse outcomes.

‡ $\chi^2$ test.

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**Table 4. RESULTS OF UNIVARIABLE AND MULTIVARIABLE LOGISTIC REGRESSION ANALYSES FOR MODEL EXCLUDING TREATMENT DURATION***

| Factor | Adjusted OR (95% CI) | *P* Value |
|---|---|---|
| Age (1-yr increments) | 1.01 (0.99-1.04) | .3 |
| Gender (reference, male) | 0.93 (0.48-1.80) | .8 |
| Disease stage (reference, stage 3) | | |
| 1 | 3.40 (1.42-8.14) | .006 |
| 2 | 2.24 (1.07-4.69) | .03 |
| Surgery (reference, nonoperative) | 28.74 (14.63-56.45) | <.0001 |

Abbreviations: CI, confidence interval; OR, odds ratio.

* After holding age and gender constant, both disease stage and treatment modality were significantly associated statistically with treatment outcome.

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patients with a more advanced age tended to have better outcomes than their younger cohorts ($P = .0058$). Patients with maxillary disease ($P = .007$) and those who had undergone surgery ($P < .0001$) also had better outcomes. Several categorical clinical factors were not related to the outcome. These included gender ($P = .06$), duration of therapy ($P = .14$), etiology of MRONJ ($P = .97$), steroid therapy ($P = .335$), and exposure to denosumab ($P = .93$ and $P = .70$), or antiangiogenics ($P = .98$).

Multivariable logistic regression analysis of the treatment outcomes and disease stage revealed a significant difference in outcomes according to the disease stage at presentation (Table 4). Patients with stage 1 or 2 disease were more likely to have better outcomes than those with stage 3 disease (stage 1, adjusted odds ratio [OR] 3.40, 1.42-8.14 confidence interval [CI], $P = .0059$; stage 2, adjusted OR 2.24, 1.07-4.69 CI, $P = .033$). Patients with disease isolated to the maxilla were 5 times more likely to have a positive outcome compared the patients with disease at other locations (unadjusted OR 5.16, 1.56-17.08 CI, $P = .007$). Also, a significant difference was found in the outcomes according to the mode of therapy. Those patients who underwent surgery were 28 times more likely to have a positive outcome than patients who had received nonoperative therapy (adjusted OR 28.74, 14.63-56.45 CI, $P > .0001$). Also, patients with malignant disease exposed to the more potent intravenous (IV) antiresorptive medications were less likely to have a positive outcome (unadjusted OR 0.58, 0.36-0.95 CI, $P > .03$).

## Discussion

The purpose of the present study was to analyze the patient data compiled from a database and assess whether the treatment outcomes were related to the demographic, staging, or other therapeutic variables. The main focus of the present retrospective study was to summarize the descriptive statistics of this patient sample and identify the factors associated with a prognosis for a good outcome.

In the present analysis, the disease stage, location of necrotic bone, and receipt of operative therapy were important factors in determining or affecting the outcome of treatment. A multiple logistic regression analysis revealed a significant difference in outcomes according to the disease stage at presentation. Patients with stage 1 or 2 disease were more likely to have better outcomes than those with stage 3 disease. These results have confirmed previous clinical observations and have verified the validity of the current staging system. Mandibular involvement was recorded in 75.4% of the patients in the present cohort. This was increased from our previous report[1] of 63% and consistent with the data from other studies,[3,4] which reported the mandible as the most common location for MRONJ. Moreover, in the present analysis, patients with disease isolated to the maxilla were 5 times more likely to have improved outcomes. This might be a reflection of the anatomic differences between the maxillary and mandibular bones.

The mode of therapy was also a significant determinant of outcome. Although the distribution of patients receiving operative or nonoperative care was similar (n = 178 [53%] operative care and n = 159 [47%] nonoperative care), the outcomes for these modes of therapy were very different. Patients who had received operative care were 28 times more likely to have a positive outcome ($P < .0001$). This finding was consistent with those from other studies reporting improved outcomes and cure rates for patients who primarily received operative care for all stages of MRONJ.[5-10]

In the descriptive analysis, the number of patients presenting with this disease process remains skewed toward women, who represented 76% of the patients in the database. This most certainly resulted from the large number of patients receiving antiresorptive therapy for osteoporosis and breast cancer, both of which are predominantly female diseases.

Despite the wide range in age, this process continues to occur mostly in the elderly population, with a mean age of 68.9 years. This finding was similar to that from other reports[3,11] and likely reflects the age range associated with the underlying disease (ie, breast cancer, multiple myeloma, osteoporosis). In the present analysis, the most elderly patients tended to do better than their younger cohorts

($P$ = .006). The significance of this finding is unclear, but might be a reflection of more aggressive disease or treatment in the younger patients.

The spectrum of diagnoses associated with ONJ has remained mostly unchanged from our original report,[1] with most patients presenting with malignancy (69.5%) and few presenting with benign disease (30.5%). This is also consistent with other reports, in which malignant disease represented the predominant underlying diagnosis for patients with ONJ.[4,11,12]

Patients with cancer and ONJ typically receive either intravenous or subcutaneous antiresorptive medications on a monthly dosing schedule. As expected, these medications were associated with 73% of the necrosis cases. Zoledronic acid exposure accounted for more than one half (57.3%) of the patients in the database. This is in contrast to data from our previous report, in which pamidronate exposure accounted for most of the cases. This difference likely resulted from a change in the prescribing practice among oncologists. Zoledronic acid was introduced as a superior alternative to pamidronate in the early part of 2001 and 2002, and since then, the use of zoledronic acid has steadily increased. In addition, the indications for antiresorptive therapy in patients with cancer have broadened to include any solid tumor with bone metastasis. Zoledronic acid therapy might become even more prevalent as data emerge suggesting a survival benefit in postmenopausal patients with breast cancer who are receiving this agent.[13-15] Zoledronic acid's potential role as an anticancer drug is likely a reflection of its inhibitory effect on circulating vascular endothelial growth factor levels and its antiangiogenic properties.[16,17]

A new database field was created in 2011 to accommodate those patients with cancer and ONJ who had had exposure to denosumab (Xgeva). Initially, most patients with ONJ who had been receiving denosumab had had a history of IV bisphosphonate therapy. Thus, it was not clear whether this was a combined effect. However, it was our observation, although not verified in the present study, that exposed bone would develop within a short period after the transition from zoledronic acid to denosumab. Eventually, the numbers of patients presenting with ONJ who were bisphosphonate naive began to increase, suggesting a relationship between denosumab and ONJ. This was also reported in all head-to-head trials of zoledronic acid versus denosumab for the treatment of osteolytic metastases in a variety of malignancies.[18-20]

In 2013, additional database fields were created to include those patients with exposure to novel targeted antiangiogenic agents, such as sunitinib (tyrosine kinase inhibitor), sorafenib (tyrosine kinase inhibitor), bevacizumab (monoclonal antibody), and everolimus (inhibitor of mammalian target of rapamycin kinase). These medications have been associated with ONJ when given in combination with antiresorptives and when administered alone.[21-24] In our database, antiangiogenic agents accounted for 24 patients (7.1%); however, only 17 subjects were not receiving concomitant antiresorptive therapy. This is similar to the results from an integrated analysis of 3 blinded trials in which 3% of the ONJ cases were associated with exposure to antiangiogenic medications.[3]

The duration of exposure appears to be related to the potency or bioavailability of the medication. The least potent or poorly adsorbed antiresorptive medications are those prescribed for the treatment of osteoporosis, and these have the longest exposure times. In our database, the number of patients with osteoporosis (n = 7) who had received denosumab were too few to make any sound assessments. As expected, the more potent antiresorptives, which are typically given intravenously or subcutaneously on a monthly schedule, had the shortest duration of exposure and represented 73% of the cases. The differences in exposure between the oral and IV bisphosphonates likely reflect the drug's bioavailability. Alendronate, for example, is a more potent bisphosphonate than pamidronate; however, its ONJ risk profile is significantly smaller. This is because oral bisphosphonates are poorly absorbed from the gastrointestinal tract, where approximately 1% of the ingested dose is absorbed into the plasma. In contrast, when a bisphosphonate is given intravenously, a much larger amount of drug is available for osseous binding and osteoclast interaction.

Among the antiresorptive agents, denosumab had the lowest exposure time; however, some of those patients were not bisphosphonate naive and had been receiving zoledronate immediately before the initiation of monthly denosumab therapy. A similar scenario exists for the antiangiogenic agents, in which only 30% of the patients were not receiving antiresorptive medications concomitantly. As more patients are encountered without previous exposure, a clearer view should emerge in the near future regarding the duration of exposure and the risk of ONJ with these drugs. The targeted antiangiogenic therapies are likely to have a different spectrum of ONJ presentation and response to therapy, because they differ so significantly from the antiresorptive agents regarding their mechanism of action and physiologic effects. Continued surveillance of patients receiving these novel medications is certainly warranted.

In the present study, an analysis of the duration of exposure as it related to the outcome was limited owing to missing or incomplete data for some subjects. As expected, short duration times were consistently noted in the descriptive analysis for the more potent medications (Table 2). However, the duration of

medication therapy did not have an effect on the outcome of treatment on univariable analysis. This finding brings into question the concept that patients with a bony reservoir of bisphosphonates have an elevated risk of a poor outcome after operative treatment strategies. In our database, the duration of therapy data did not consider the various medication schedules. In future analyses, the cumulative dose load will also be monitored to further clarify this variable.

In contrast to other studies and our previous report in 2004,[1] the present cohort of patients had a larger proportion of bone exposures that were spontaneous (42.5%) and not preceded by a surgical procedure. It would be interesting to determine how many of these patients with spontaneous exposures were denture wearers, because denture trauma or trauma related to mastication without the denture in place might not have been captured. The number of spontaneous cases of MRONJ underscores the importance of surveillance for patients receiving these medications.

More than twice as many patients presented with stage 2 disease as stage 1 or stage 3, similar to that reported by other studies.[25] With the exception of the stage 0 category, a more recent addition to the database, the distribution of cases within the 3 stages has been fairly constant.

The strength of the present study was that the data input and all aspects of the clinical follow-up and treatment data were performed solely by us. Patient data that were submitted but not verified by clinical examination were not included in the present study. This allowed for consistent long-term follow-up monitoring by a single surgeon for all the subjects with data in the database. The data fields were routinely updated to reflect the evolving trends in management strategies and to capture additional medications associated with the development of ONJ. The analysis of patients exposed to antiangiogenic medication was also limited owing to the relatively small number of subjects receiving those medications. This will be a focus of future studies as the number of patients receiving this mode of therapy increases.

## References


1. Ruggiero S, Mehrotra B, Rosenberg T: Osteonecrosis of the jaws associated with the use of bisphosphonates: A review of 63 cases. J Oral Maxillofac Surg 62:527, 2004
2. Ruggiero S, Dodson T, Fantasia J, et al: American Association of Oral and Maxillofacial Surgeons paper on medication-related osteonecrosis of the jaw—2014 Update. J Oral Maxillofac Surg 72: 1938, 2014
3. Saad F, Brown JE, Van Poznak C, et al: Incidence, risk factors, and outcomes of osteonecrosis of the jaw: Integrated analysis from three blinded active-controlled phase III trials in cancer patients with bone metastases. Ann Oncol 23:1341, 2012
4. Mavrokokki T, Cheng A, Stein B, Goss A: The nature and incidence of bisphosphonate associated osteonecrosis of the jaws in Australia. J Oral Maxillofac Surg 3:415, 2007
5. Carlson E, Basile J: The role of surgical resection in the management of bisphosphonate-related osteonecrosis of the jaws. J Oral Maxillofac Surg 67:85, 2009
6. Eckardt A, Lemound J, Lindhorst D, et al: Surgical management of bisphosphonate-related osteonecrosis of the jaw in oncologic patients: A challenging problem. Anticancer Res 31:2313, 2011
7. Graziani F, Vescovi P, Campisi G, et al: Resective surgical approach shows a high performance in the management of advanced cases of bisphosphonate-related osteonecrosis of the jaws: A retrospective survey of 347 cases. J Oral Maxillofac Surg 70:2501, 2012
8. Mucke T, Koschinski J, Deppe H, et al: Outcome of treatment and parameters influencing recurrence in patients with bisphosphonate-related osteonecrosis of the jaws. J Cancer Res Oncol 137:907, 2011
9. Stanton DC, Balasanian E: Outcome of surgical management of bisphosphonate-related osteonecrosis of the jaws: Review of 33 surgical cases. J Oral Maxillofac Surg 67:943, 2009
10. Stockman P, Vairaktaris E, Wehrhan F, et al: Osteotomy and primary wound closure in bisphosphonate-associated osteonecrosis of the jaw: A prospective clinical study with 12 months follow-up. Support Cancer Care 18:449, 2009
11. Yamazaki T, Yamori M, Ishizaki T, et al: Increased incidence of osteonecrosis of the jaw after tooth extraction in patients treated with bisphosphonates: A cohort study. Int J Oral Maxillofac Surg 41:1397, 2012
12. Tsao C, Darby I, Ebeling PR, et al: Oral health risk factors for bisphosphonate-associated jaw osteonecrosis. J Oral Maxillofac Surg 71:1360, 2013
13. Coleman R, Cameron D, Dodwell D: Adjuvant zoledronic acid in patients with early breast cancer: Final efficacy analysis of the AZURE (BIG 1/04) randomised open-label phase 3 trial. Lancet 15:997, 2014
14. Coleman R, Marshall H, Cameron D, et al: Breast-cancer adjuvant therapy with zoledronic acid. N Engl J Med 365:1396, 2011
15. Gnant M, Mlineritsch B, Schippinger W, et al: Endocrine therapy plus zolendronic acid in premenopausal breast cancer. N Engl J Med 360:679, 2009
16. Fournier P, Boissier S, Filleur S, et al: Bisphosphonates inhibit angiogenesis in vitro and testosterone-stimulated vascular regrowth in the ventral prostate in castrated rats. Cancer Res 62:6538, 2002
17. Wood J, Bonjean K, Ruetz S: Novel antiangiogenic effects of the bisphosphonate compound zolendronic acid. J Pharm Exp Ther 302:1055, 2002
18. Lipton A, Fizazi K, Stopeck AT, et al: Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: A combined analysis of 3 pivotal, randomised, phase 3 trials. Euro J Cancer 48:3082, 2012
19. Henry D, Costa L, Goldwasser F, et al: A double-blind, randomized study of denosumab versus zoledronic acid for the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate) or multiple myeloma. J Clin Oncol 29:1125, 2011
20. Fizazi K, Carducci M, Smith M, et al: Denosumab versus zoledronic acid for the treatment of bone metastases in men with castration-resistant prostate cancer: A randomized, double-blind study. Lancet 377:813, 2011
21. Guarneri V, Miles D, Robert N, et al: Bevacizumab and osteonecrosis of the jaw: Incidence and association with bisphosphonate therapy in three large prospective trials in advanced breast cancer. Breast Cancer Res Treat 122:181, 2010
22. Koch F, Walter C, Hansen T, et al: Osteonecrosis of the jaw related to sunitinib. J Oral Maxillofac Surg 15:63, 2011
23. Christodoulou C, Pervena A, Klovas G, et al: Combination of bisphosphonates and antiogenic factors induces osteonecrosis of the jaw more frequently than bisphosphonates alone. Oncology 76:209, 2009
24. Smidt-Hansen T, Folkmar T, Fode K, et al: Combination of zoledronic acid and targeted therapy is active but may induce osteonecrosis of the jaw in patients with metastatic renal cell carcinoma. J Oral Maxillofac Surg 71:1532, 2013
25. Bagan JV, Hens-Aumente E, Leopoldo-Rodado M, et al: Bisphosphonate-related osteonecrosis of the jaws: Study of the staging system in a series of clinical cases. Oral Oncol 48:753, 2012